Air Pollution and Adverse Birth Outcomes in the South Coast Air Basin, 1989-2000

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& Environmental Health Sciences

Why Study Air Pollution and Pregnancy?

- Developing organism is uniquely sensitive to environmental toxins within a short time window
- Adverse outcomes are common; in US:
  - ~10% are preterm
  - ~ 5% are low weight
- Immediate and long term health effects
  - Infant morbidity and mortality
  - Adverse effects on adult health?

Research Advantages

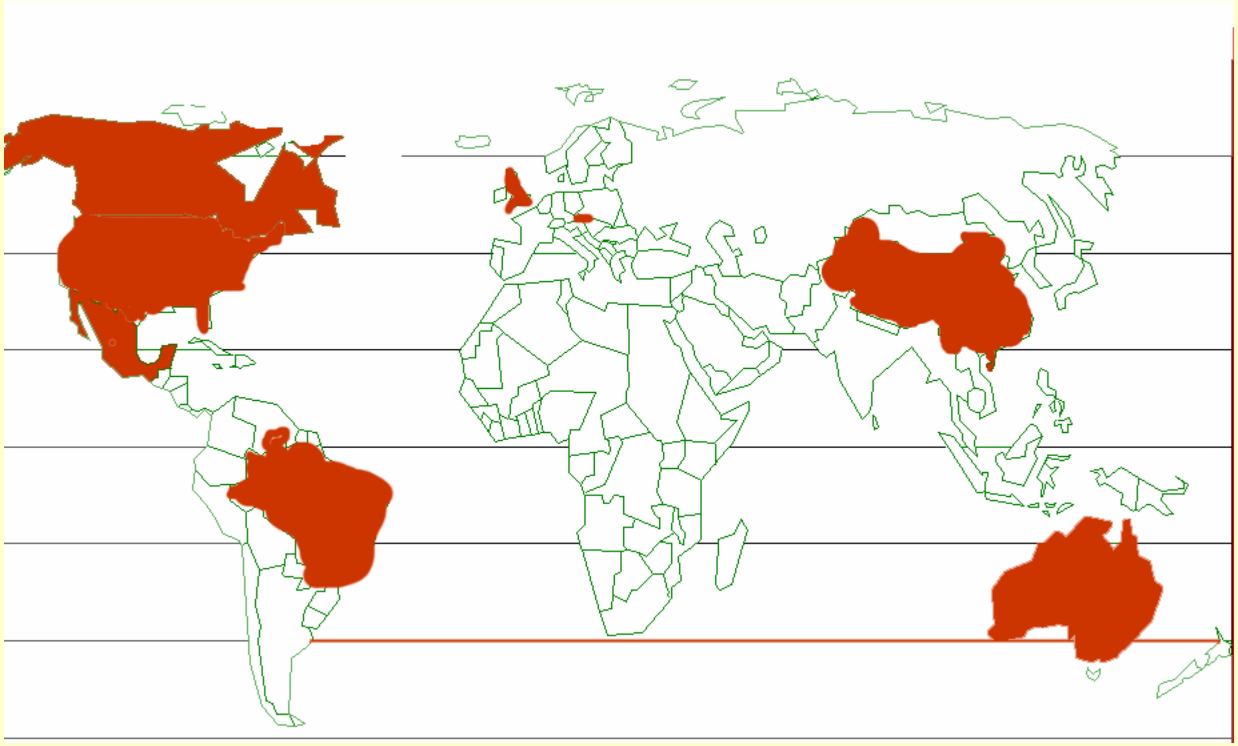
In many urban areas:

- Electronic birth registry data available
  - Source of information on outcomes (LBW/preterm birth), potential confounders, and residential location at birth
- Existing networks of government monitoring stations
- Large number of births
  - E.g.,125,000 births in a 5 year period in 37 LA zip code areas near government air monitors
- Vulnerable periods for specific adverse events are brief and generally well-defined

Pregnancy and ambient air pollution recently has become a focus of studies worldwide

Studies were conducted in

Australia, Brazil, Canada, China, Czech Republic, Great Britain, S. Korea, Mexico, United States…



Outcome Events Studied

- Low birth weight (LBW)
  - Weight at birth <2500g
  - Born LBW at term *vs.* preterm
  - Reduction in mean weight
  - Small for gestational age (SGA; <10th percentile of weight for gestational age)
- Length and head circumference
- Preterm birth (<37 weeks of gestation)
- Malformations (cardiac and cleft)

Exposure Assessment

Mostly:

- Criteria air pollutants (CO, NO_2, PM_{10}, $PM_{2.5}$, SO_2, O_3) measured at ambient monitoring stations:
  - Annual or daily area-wide averages
  - Average over gestational period of interest from monitor closest to maternal residence

Rarely or in small samples:

Air toxics:

- PAH-DNA adduct concentrations in umbilical cord blood
- Modeled POM concentrations
- Personal PAH measurements

Studies of Term Low Birth Weight

Study	**Dates**	**Location**	**Pollutants**
Wang et al. (1997)	1988-91	Beijing, China	TSP, SO_2
Ritz and Yu (1999)	1989-93	Southern CA, USA	CO, PM_{10}, NO_2, O_3
Maisonet et al. (2001)	1994-96	6 NE cities, USA	CO, PM_{10}, SO_2
Ha et al. (2001)	1996-97	Seoul, South Korea	CO, PM_{10}, NO_2, SO_2, O_3
Lee et al. (2003)	1996-98	Seoul, South Korea	CO, PM_{10}, NO_2, SO_2
Wilhelm and Ritz (2005)	1994-00	Southern CA, USA	CO, PM_{10}, NO_2, O_3

Studies of Term Low Birth Weight

- Associations most consistently reported for CO, particles (TSP, PM_{10}), SO_2 averaged over 3rd trimester

- Reported increases in risk <50%, large differences in Δ pollutant concentrations estimates represents

  - E.g., 10% increase per 100 $\mu g/m^3$ TSP (China) vs. 36% increase per 10 $\mu g/m^3$ PM_{10} (SoCAB)

Studies of Preterm Birth

Study	Dates	Location	Pollutants
Xu et al. (1995)	1988-91	Beijing, China	TSP, SO_2
Ritz et al. (2000)	1989-93	Southern CA, USA	CO, PM_{10}, NO_2, O_3
Bobak (2000)	1991	Czech Republic	TSP, SO_2, NO_x
Vassilev et al. (2001)	1990-91	New Jersey, USA	POM (including PAHs)
Maroziene and Grazuleviciene (2002),	1998	Kaunas, Lithuania	NO_2, formaldehyde
Woodruff et al. (2003)	1998-99	USA	CO, PM_{10}, NO_2, O_3, SO_2
Liu et al. (2003)	1985-98	Vancouver, Canada	CO, NO_2, O_3, SO_2
Wilhelm and Ritz (2005)	1994-00	Southern CA, USA	CO, PM_{10}, NO_2, O_3

Studies of SGA

Study	Dates	Location	Pollutants
Dejmek et al. (1999)	1994-96	Czech Republic	PM_{10}, $PM_{2.5}$
Dejmek et al. (2000)	1994-98	Czech Republic	PM_{10}, $PM_{2.5}$, PAHs
Vassilev et al. (2001)	1990-91	New Jersey, USA	POM (including PAHs)
Liu et al. (2003)	1985-98	Vancouver, Canada	CO, NO_2, O_3, SO_2

- **Large increases reported for PM exposures during first month of pregnancy**
  - **264% increase for ≥50 ug/m³ vs. <40 ug/m³ PM_{10}, 211% increase for ≥37 ug/m³ vs. <27 ug/m³ $PM_{2.5}$**
- **Due to toxic action of PAHs sorbed to particles?**
  - **Czech Republic: 22% increase per 10 ng/m³ PAHs**

Biologic Mechanism?

Some animal data suggests fetus may be vulnerable to CO

- With sufficient time fetal COHb levels surpass maternal levels due to longer wash-out period

However, are ambient CO levels sufficient to cause harm?

Ultrafine particles can adsorb toxins (PAHs, hydroquinones etc) and reach the placenta and fetus

- Disrupt trophoblast formation and placental function
- Cause infections or inflammation in mother
- Interfere with hypothalamic-pituitary-placental axis
- Damage fetal tissues?

PAHs – Possible Mechanism?

- PAH-DNA adduct levels in maternal blood and placentas higher in areas with higher air pollution (Sram et al. 1999, Whyatt et al., 1998)

- Exposure to extracts of urban air PM increased DNA adducts and embryotoxicity *in vitro* (Binkova et al., 1999, 2003)

- Perera et al. (1998), Krakow and Limanowa Poland, 1992
  - 147 g in bw, 1.1 cm in bl, 0.9 cm in hc for >$3.85/10^8$ nucleotides PAH-DNA adducts in umbilical cord blood leukocytes

- Perera et al. (2003), New York, USA, 1997-98
  - 9% in bw, 2% in hc for ≥ 2.7 ng/m^3 vs. <2.7 ng/m^3 personal PAH exposures among African-American women (48-hr average during 3rd trimester)

Limited Comparability of Studies

- Differences in:
  - Outcome definitions
  - Air pollutants measured
  - Scaling of units for pollutants
  - Timing of exposure (correct pregnancy period?)
  - Covariates included in models
  - Air pollution sources

Moving Forward….

- Improve exposure assessment
  - Need additional neighborhood/personal air monitoring data to examine:
    - Intra-community variability in pollutant concentrations
    - Time-activity patterns
    - Indoor and in-transit exposures
- Determine biologic mechanisms of action
  - Additional toxicologic data needed to identify pathways and pollutants of concern

Air Pollution and Adverse Birth Outcomes in the SoCAB

Summary of Research

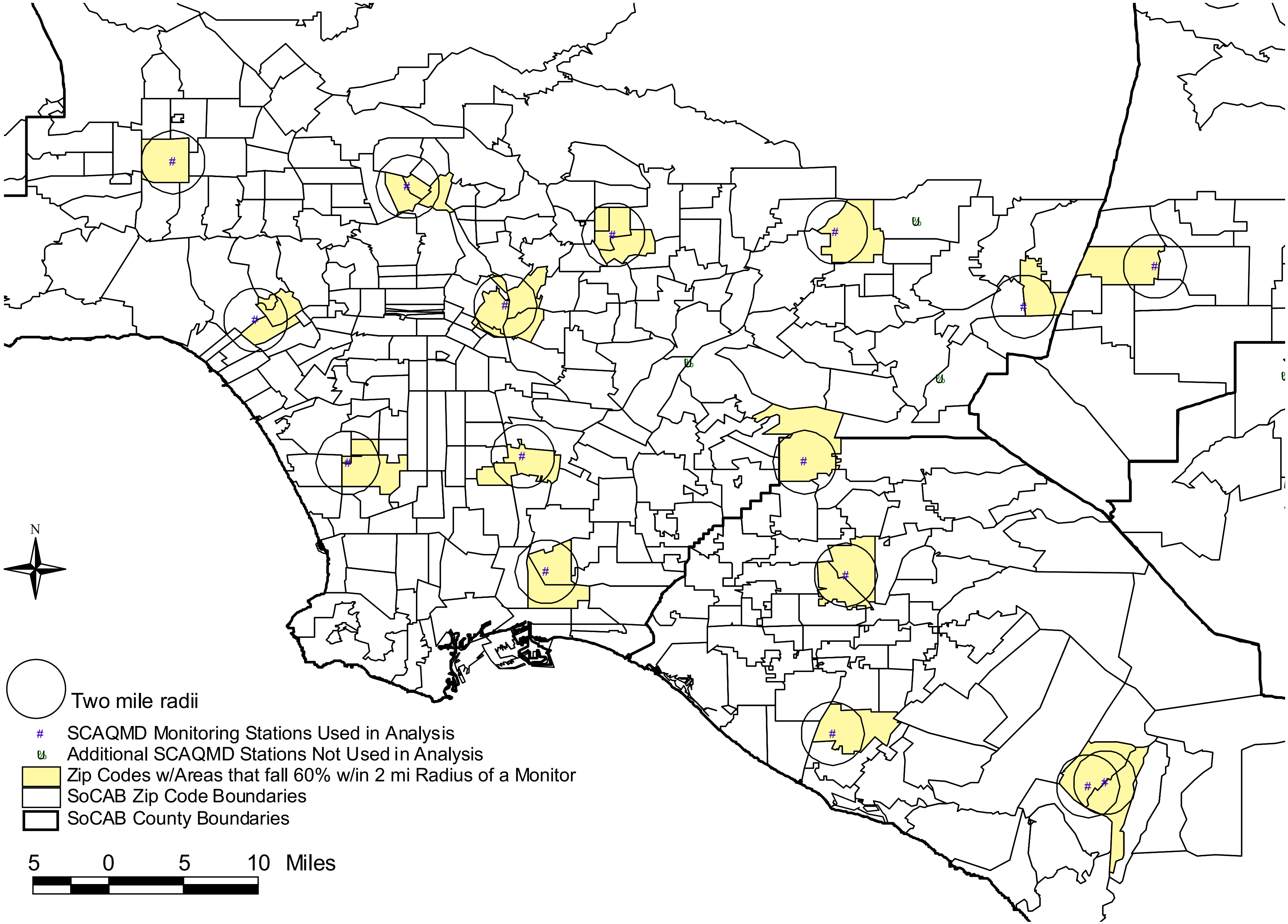
Why the South Coast Air Basin

- Large number of births (~ half of all CA births, most in LA county)
- Birth certificates are readily available
- Dense air pollution monitoring network

Exposure assessment for 1989-1993 study

- Mothers residing within a 2-mile radius of stationary ambient CO (PM-10) monitors at the time of birth (relaxed this criterion for birth defects)
- For each child we calculated the last trimester or last 6 week etc average CO (PM-10) using the closest ambient monitoring station

Map of SCAQMD Monitoring Stations and Zip Codes Included in Analysis



Risk Factors for Preterm Birth and/or Low Birth Weight (LBW)

Controlled for in the analysis

- birth type (single or other)
- parity
- sex of the infant
- maternal age
- maternal ethnicity
- maternal educational attainment
- delivery interval <12 months
- prenatal care
- (transportation time to work (from census data))

Risk Factors Not Reported on Birth Certificates

<u>not</u> controlled for in the analysis

- pre-pregnancy weight, weight gain, and height of mother
- history of loss of the most recent pregnancy
- social factors (marital status?, occupational exposures to toxins?)
- behavioral factors (e.g. smoking, caffeine use, marihuana smoking, alcohol drinking during pregnancy)

Adjusted Odds Ratios (95%CI) for Term LBW
3rd trimester ambient CO levels

1989-1993, 18 monitoring stations in SoCAB

	All children *case N=2,809* *non-case N=122,7640*	**Higher parity children** *case N=1,454* *non-case N=73,687*	**Young Women** *case N=420* *non-case N=15,111*
CO-level (ppm):			
- 2.2	1.0	1.0	1.0
- 2.2 - <5.5	1.04 (0.96, 1.13)	1.03 (0.92, 1.15)	1.02 (0.83, 1.26)
- 5.5	1.22 (1.03, 1.44)	1.33 (1.07, 1.65)	1.54 (1.07, 2.22)

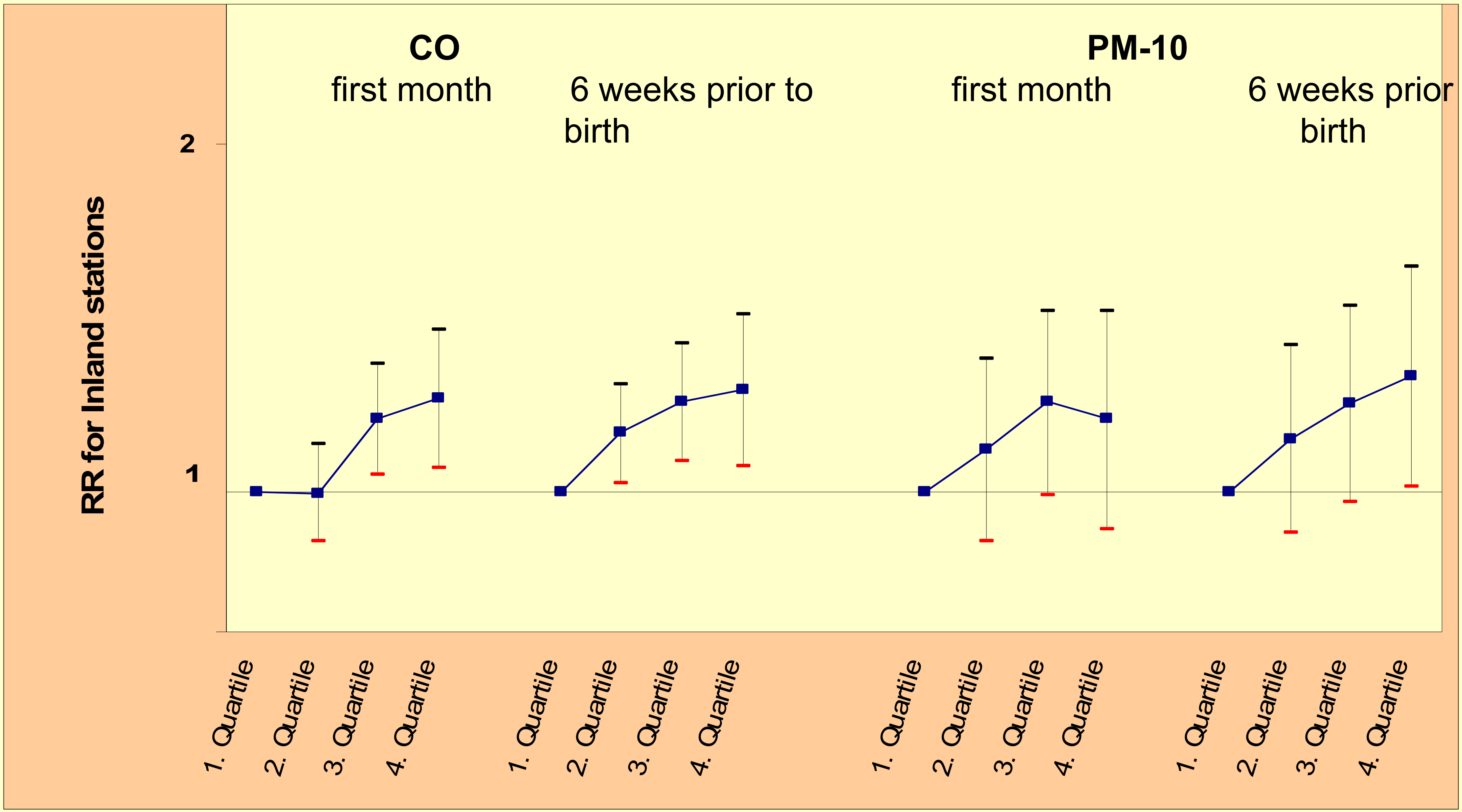
Adjusted Odds Ratios (95%CI) for Term LBW

Ambient CO levels at South Central LA station only, 1989-1993

	First Trimester 2-mile	Second Trimester 2-mile radius	Third Trimester 2-mile radius	Third Trimester 5-mile radius
CO level:				
- 50th percentile	1.0	1.0	1.0	1.0
- 50-95th percentile	0.87 (0.73-1.03)	1.02 (0.85-1.20)	1.06 (0.89-1.26)	1.07 (0.99-1.16)
- 95th percentile	0.82 (0.54-1.24)	0.97 (0.65-1.44)	1.24 (0.87-1.77)	1.24 (1.06-1.45)

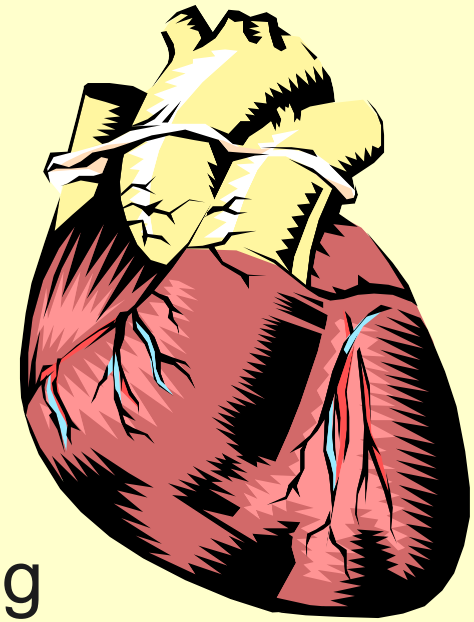
2 mile radius: case N=572, non-case N=23,533;
5 mile radius: case N=2,805, non-case N=94,160

Adjusted Rate Ratios (95% CI) for Preterm Birth by Quartile of Ambient CO and PM-10 (9 Inland Stations only)



Cardiac Malformations

- Data from CA Birth Defect Monitoring Program (1989-1993)
- Evaluated 6 different common
- heart defects
- Exposure based on ambient
- monitoring station data during
- first 3 months of pregnancy for each infant



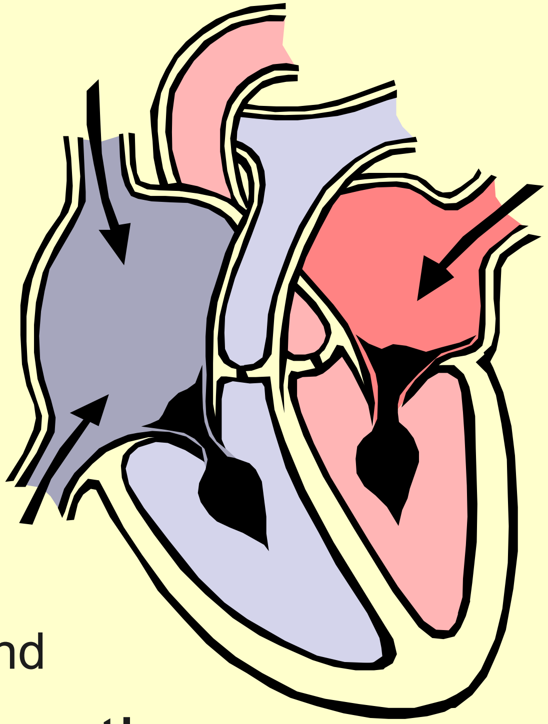
Pregnancy month	Odds Ratios (95% CI) adjusted for covariates *	
CO (ppm)	Case N=234 Control N=7944	
1st month		
<1.14	1	-
1.14-<1.60	1.05	0.66-1.68
1.60-<2.47	1.12	0.59-2.12
>=2.47	1.23	0.53-2.82
2nd month		
<1.14	1	-
1.14-<1.57	1.63	1.00-2.66
1.57-<2.39	1.97	1.00-3.91
>=2.39	2.84	1.15-6.99
3rd month		
<1.12	1	-
1.12-<1.51	0.77	0.49-1.22
1.51-<2.27	0.54	0.29-1.02
>=2.27	0.70	0.31-1.58

CO and (isolated) Ventricle Septum Defects

(multi-pollutant model)

Cardiac Malformations: Results

- Risk of certain cardiac heart defects was increased at high exposure levels
  - Ventricle septum birth defects (CO)
  - Aortal and pulmonary artery and valve defects (Ozone)
- Increased risks were observed in 2nd month of pregnancy when heart formation occurs



Results Summary SoCAB1989-1993

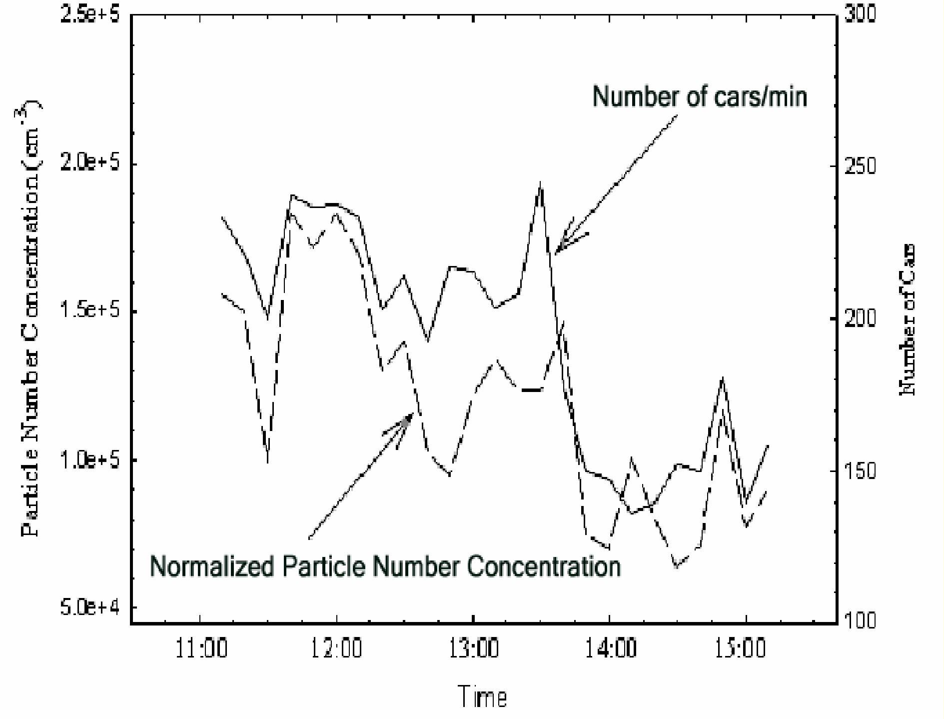
[Ritz et al. 1999, 2000, 2001]

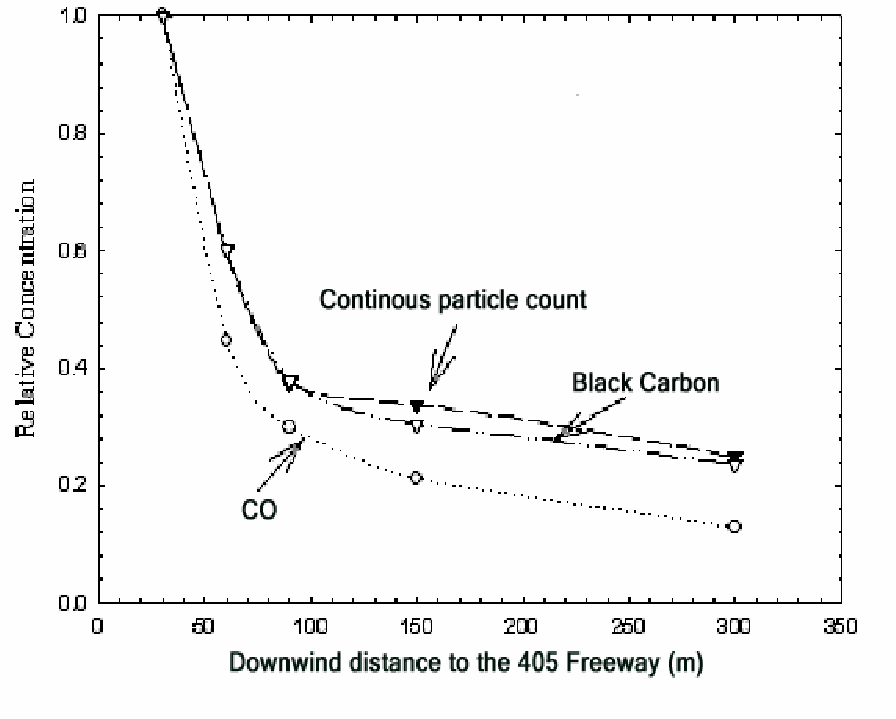
Increased Risks for

- CO and term low birth weight (third trimester)
- CO/PM-10 and preterm birth (6 weeks prior to birth)

- CO and cardiac ventricular septal birth defects
- Ozone and aortic/pulmonary artery and valve anomalies, and conotruncal birth defects
  - Dose-response in 2nd month of pregnancy

Is CO a marker for traffic related pollution?





Y. Zhu and W. Hinds, UCLA Particle center

Epidemiologic studies ignore potential spatial heterogeneity of vehicle-related air pollution when using exposure data from ambient air monitoring stations

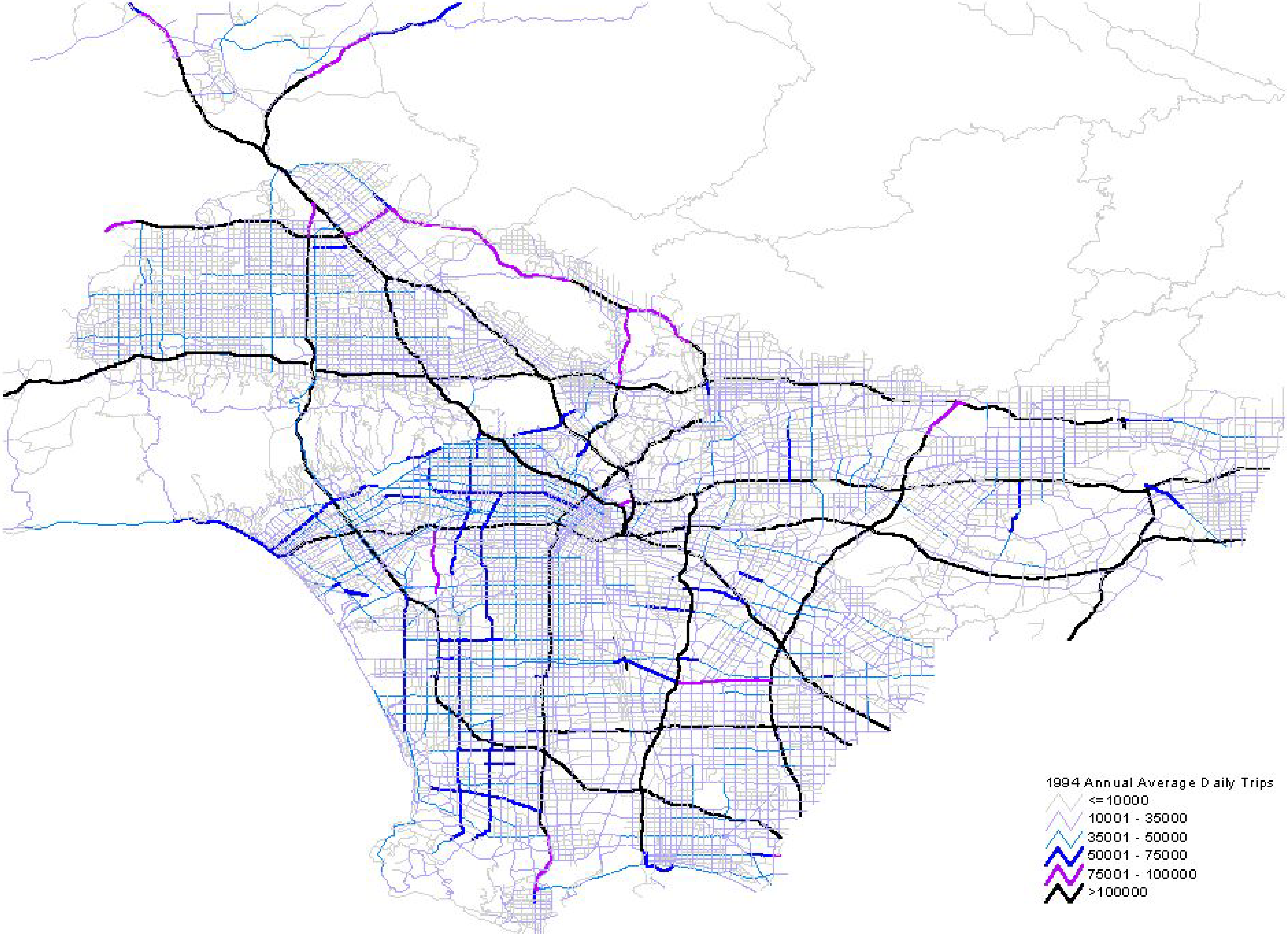
Traffic Density

How can we estimate traffic-related contributions using existing data for large areas?

Simple TD measures used in previous Epi studies

- Self-reported traffic density on street of residence
- Residential distance to major roads/freeways
- Measured traffic density on main roads near homes
- Average traffic density in wards

1994 Caltrans AADT Data - LA County

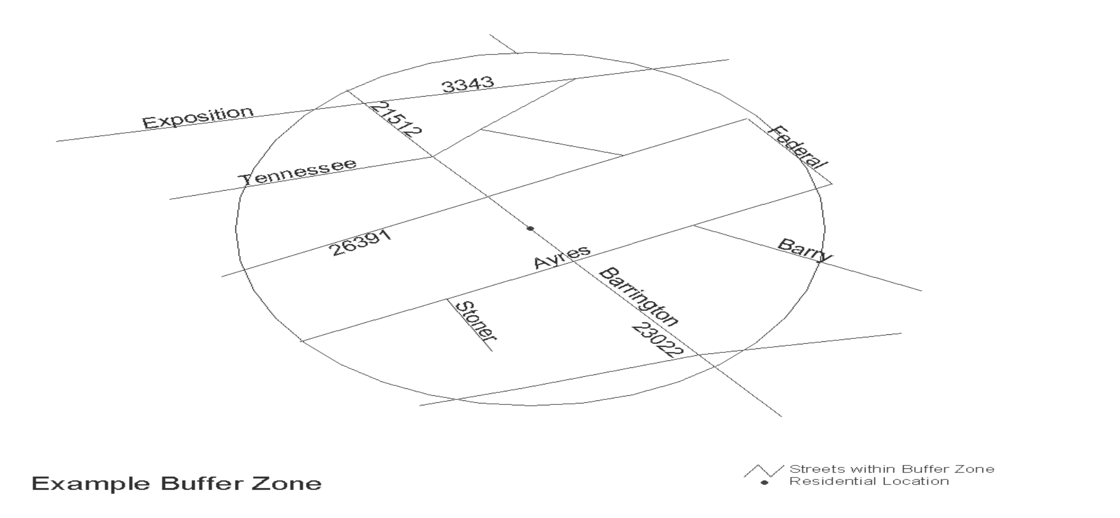


Traffic Density

More sophisticated TD measures

- Distance weighted traffic density (DWTD)
  - Traffic count on all streets within a certain radius of home weighted by distance from road
- Air dispersion models (e.g. Caline4, IMMIS-Luft)
  - Incorporates emission levels, road geometry, meteorology

Distance Weighted Traffic Density



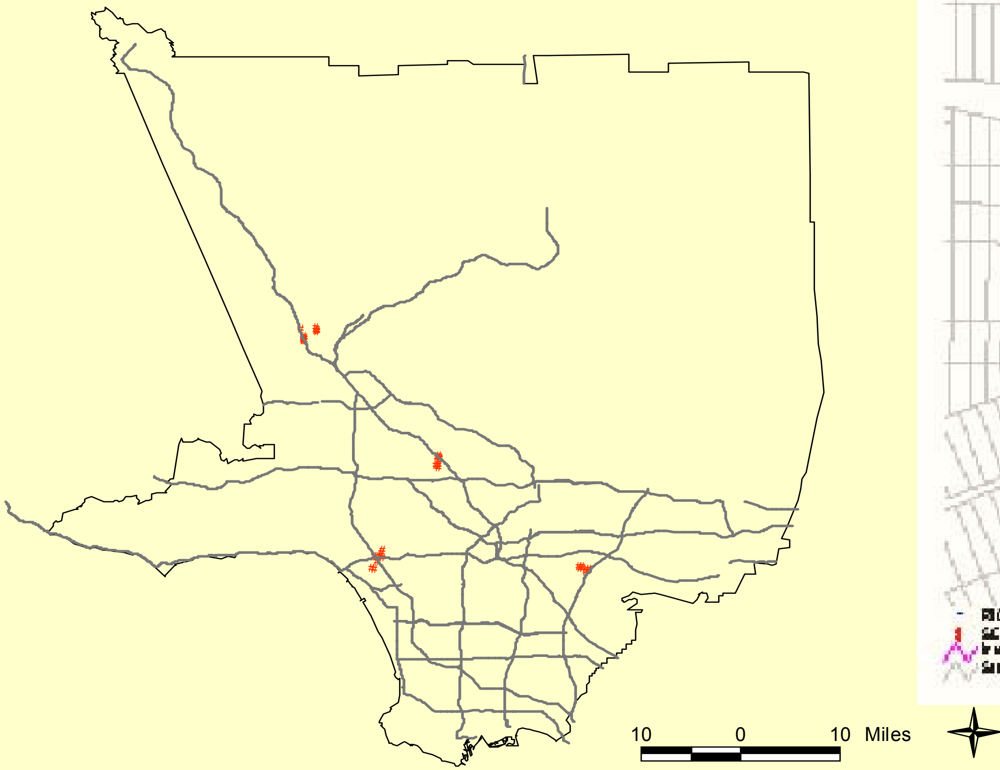
DWTD value calculated for each subject

- for all streets within 750 ft. buffer of home
- traffic counts on each street weighted by distance of home to street (using a Gaussian distribution)
- summed over weighted counts for all streets in buffer

RIOPA study

Measurement of Indoor and Outdoor CO Concentrations at 56 LA Homes in Two Seasons

Four RIOPA Community Locations in Los Angeles County, CA



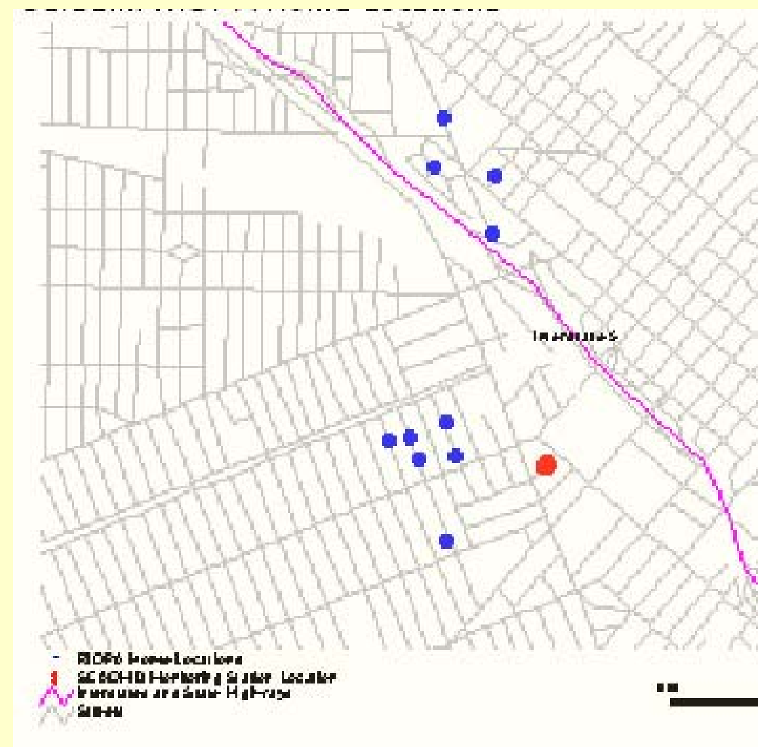
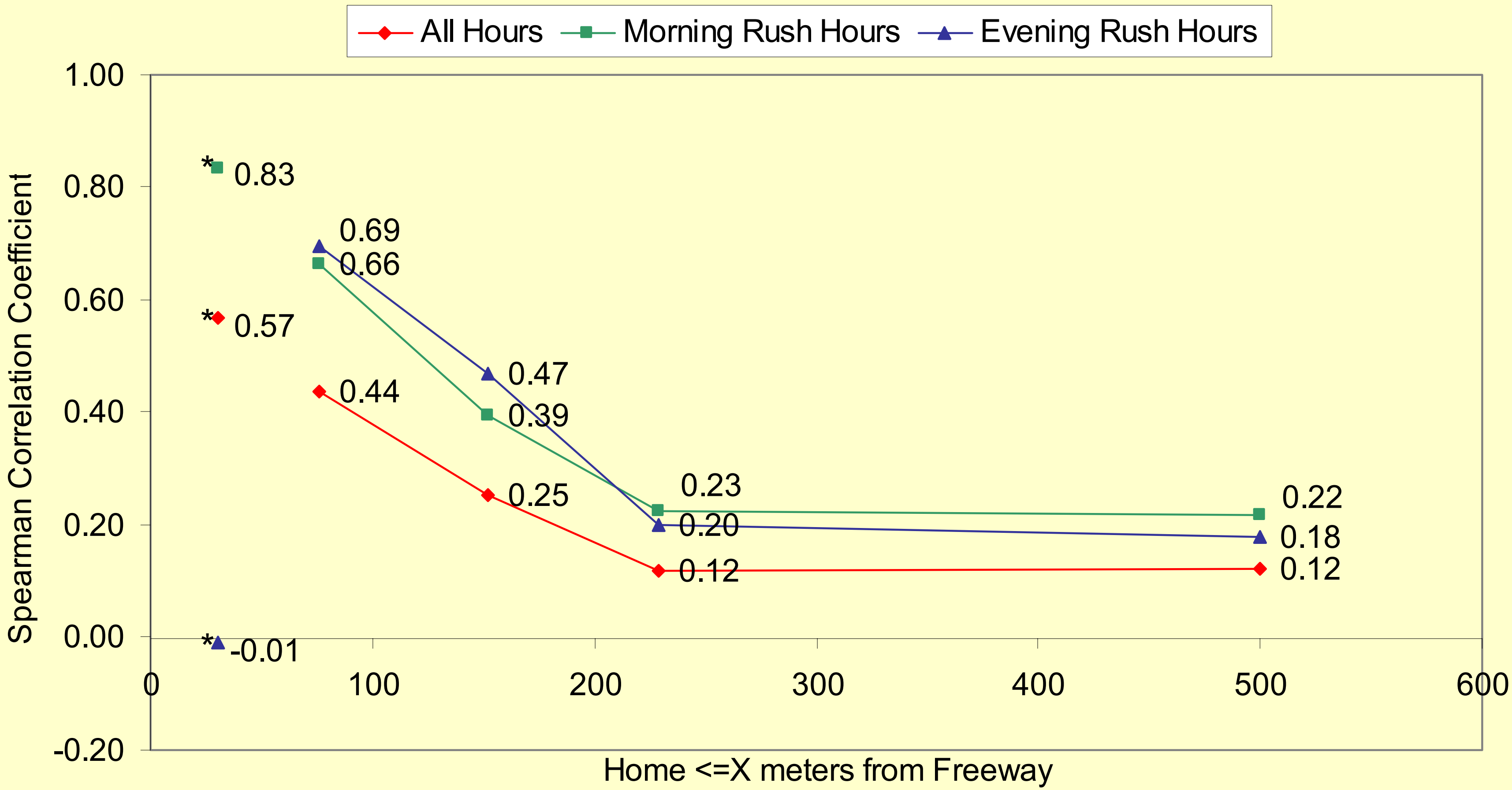
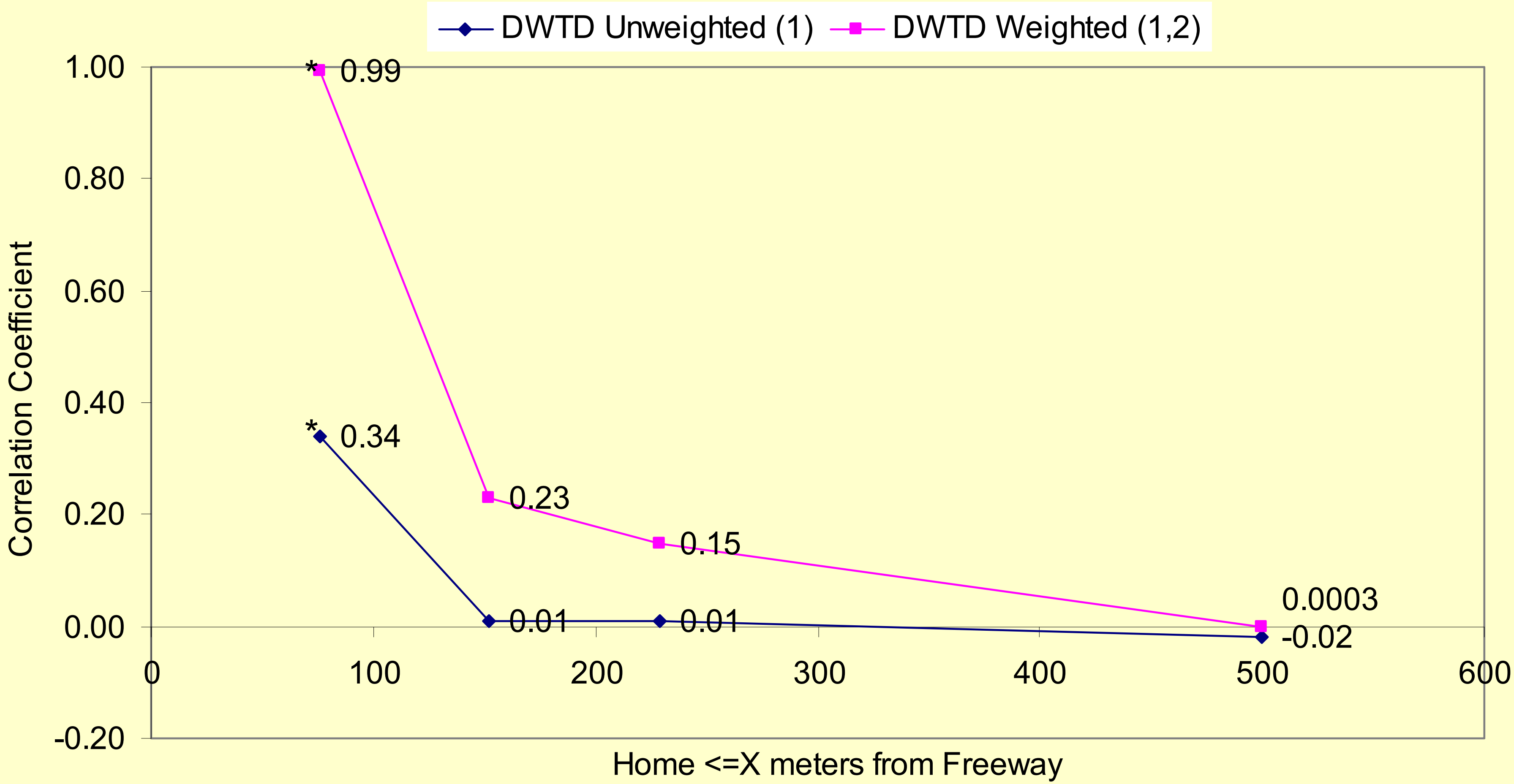


Figure 3a. Correlation Between Hourly Indoor CO Concentrations (ppm) and Hourly Freeway Traffic Counts



*Note: Results in last distance category (<=30.48m) based on data from two sampling periods at a home with indoor CO sources present (attached carport, furnace, and possibly smoking).

Figure 4b. Correlation Between 48-Hour Average Outdoor CO Concentrations (ppm) and DWTD Values



1 The DWTD value is based on an annual average 24-hour traffic count.

2 Street-specific DWTD values adjusted by percent of time home w as dow nw ind of street.

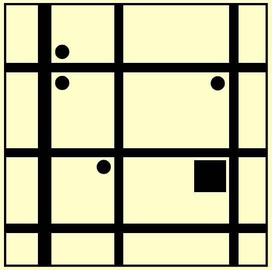
*Note: Results in last distance category (<=76.2m) based on n=3 48-hour averages.

Methods

For 1994-96, in 112 LA zip codes, we identified all

- term low birth weight (LBW) and
- preterm infants

(Case N=31,191) and a random sample of controls (~ same N)



Mapped residential birth addresses using GIS (ESRI StreetMap)

~86% had electronic address data;

of those ~91% could be mapped

Transferred Caltrans annual average daily traffic (AADT) count data for each year on to ESRI StreetMap

Methods

Covariates

- **All** models included (from birth records):
  - Access to prenatal care; maternal age, race, education; infant sex; parity; gestational age (for LBW); interval to last live birth (for preterm); year of birth

- **Some** models included:
  - Background ambient air pollution concentrations (annual averages)
  - One or more freeways within buffer zone
  - Census-tract SES indicators (1990 U.S. Census):

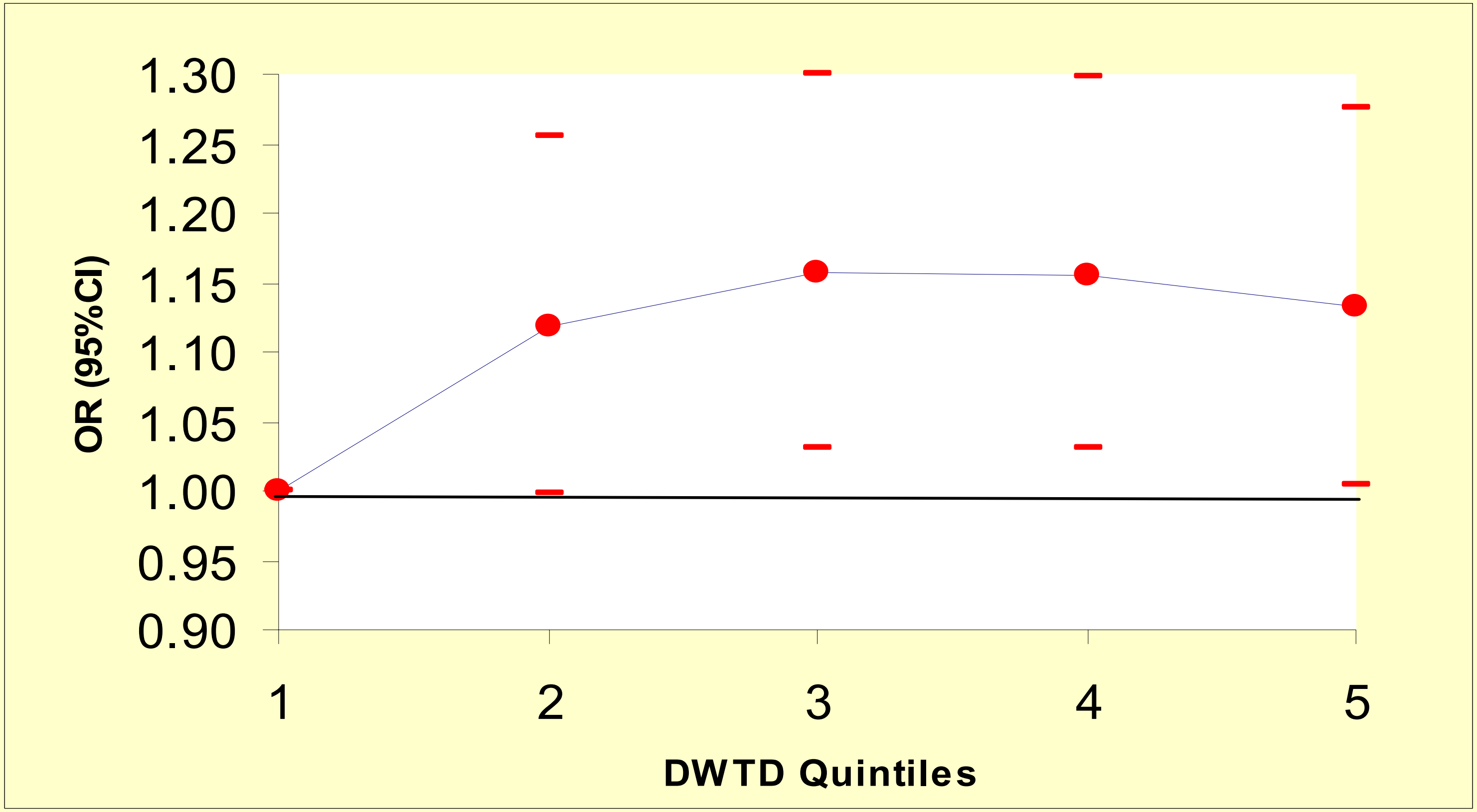
    household or per capita income, building age, home value, gross rent, % of children in poverty

Results

DWTD and Term Low Birth Weight

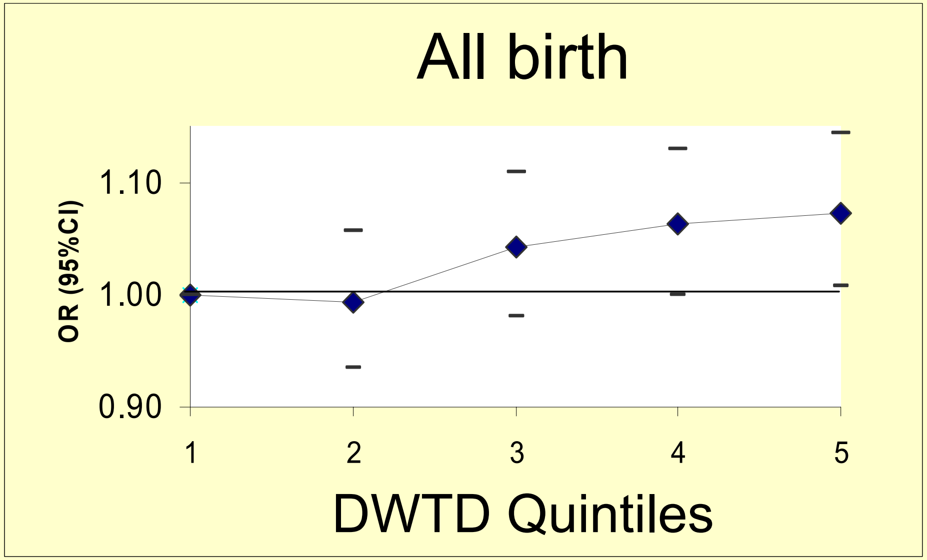
Case N=3,736; Control N=26,196

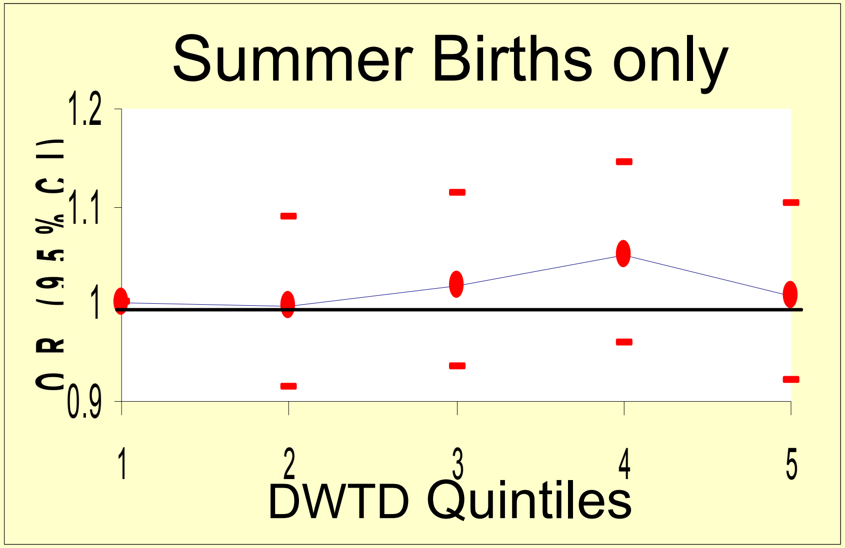
*twins/triplets excluded

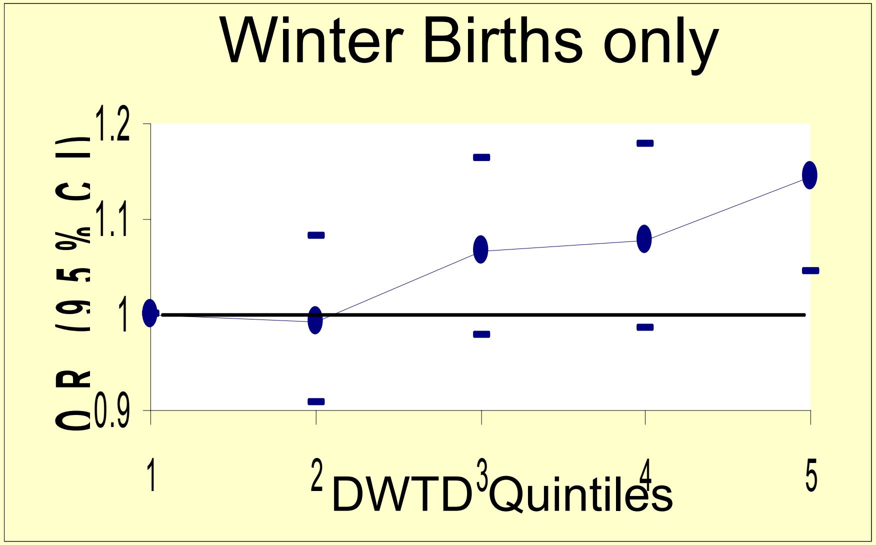


Results

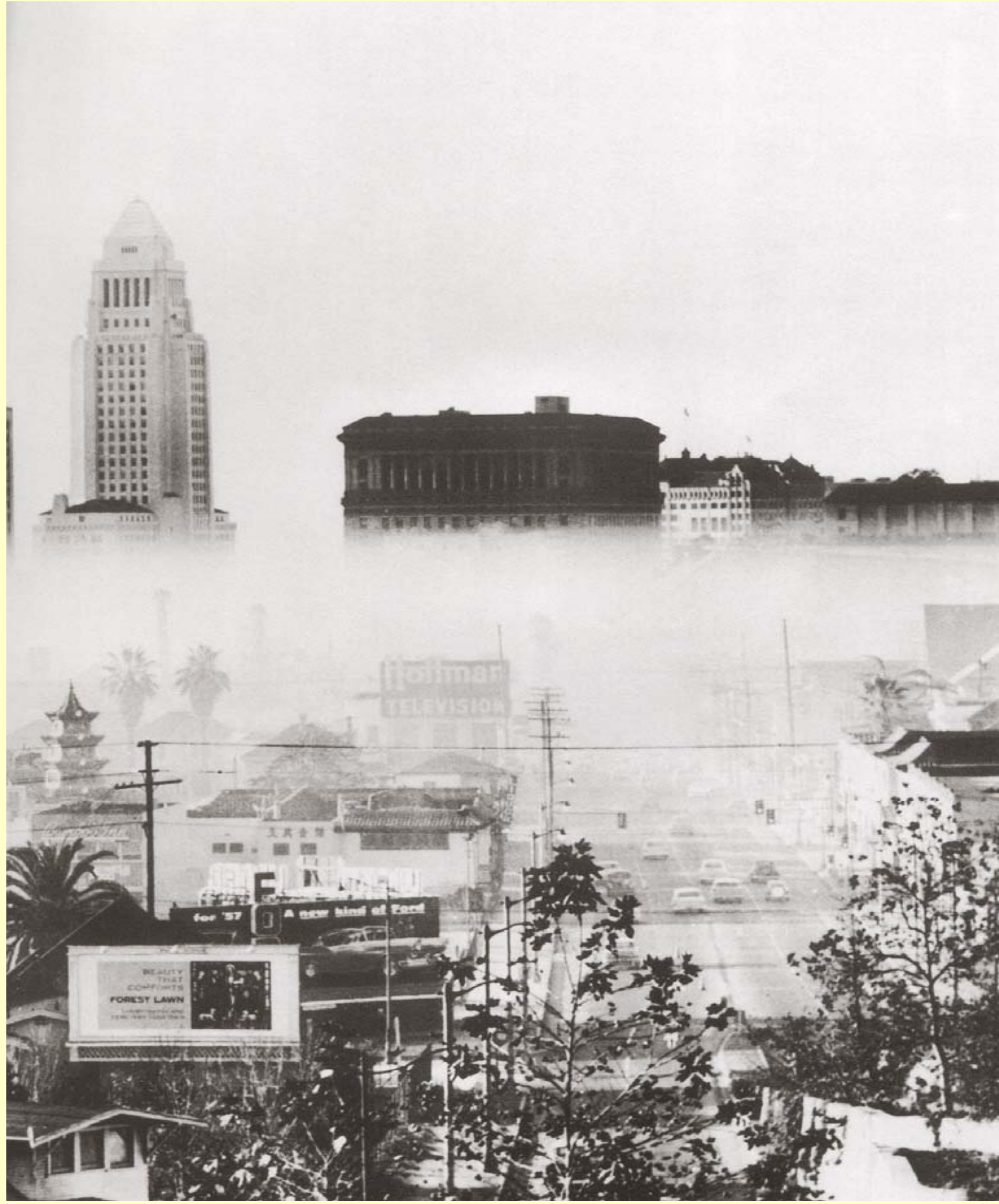
DWTD and Preterm Birth (Case N=17,706; Control N=26,005)







Low inversion layers trap pollutants in colder seasons?



Conclusions

- In LA, risks of term LBW and preterm birth increase with DWTD
  - Various census-tract level indicators of SES did not change estimates
- Greater risks in
  - winter births
  - areas with higher background air pollution (ambient CO and PM)

New Study SoCAB 1994-2000

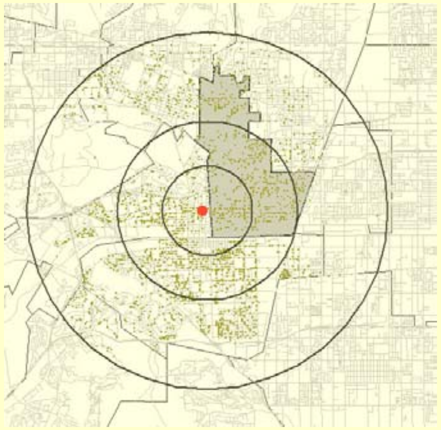
Goals:

- Perform analyses for all births in 1994-2000:
  - Singleton Term LBW
  - Singleton, Vaginally-delivered Preterm Infants

- Evaluate additional pollutant:
  - PM2.5 – monitoring began in SoCAB during 1999

- Compare results using
  - for varying distances from a monitoring station

Zip Code *vs.* Address



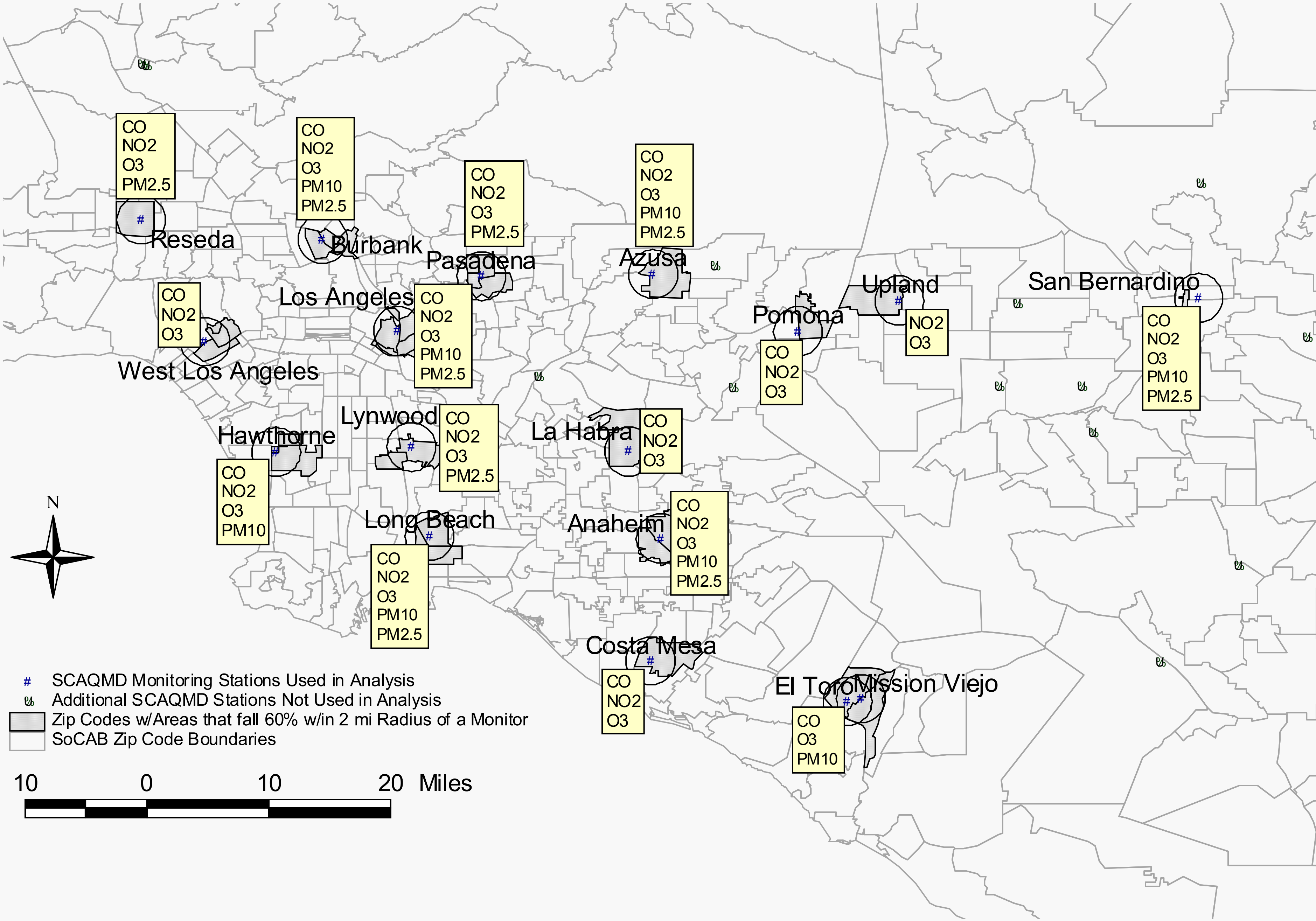
Zip code:

- Selected all births in zip codes within a 2-mile radius of an ambient monitoring station ($\geq$60% of area)

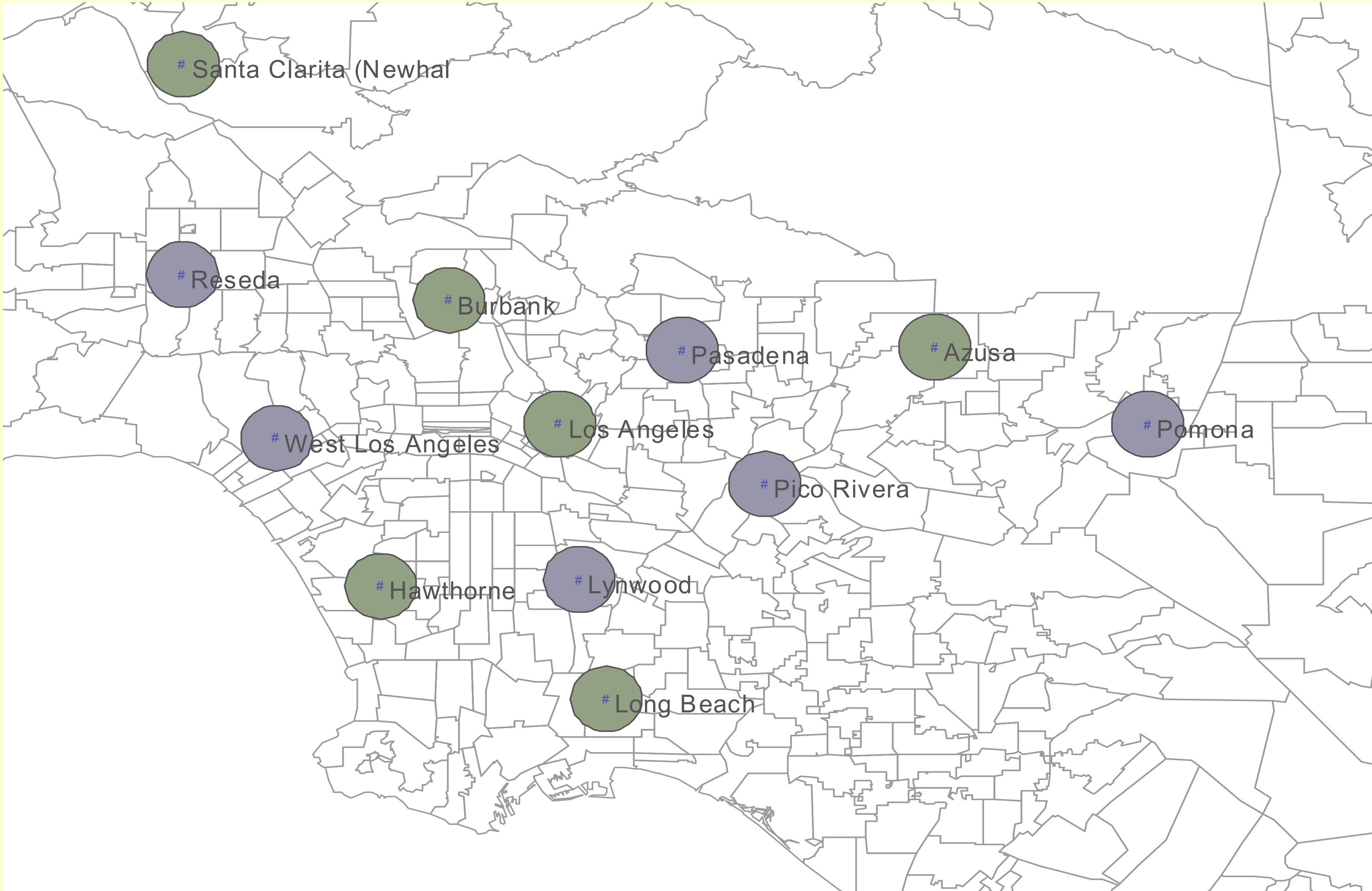
Address:

- Selected all births in zip codes within a 4-mile radius of a monitoring station
- Obtain electronic address data (L.A. County)
  - Address was available for 81-97% of subjects (varies by year)
- Mapped residential birth addresses using GIS (ESRI StreetMap™)
  - 89-91% of subjects could be geocoded

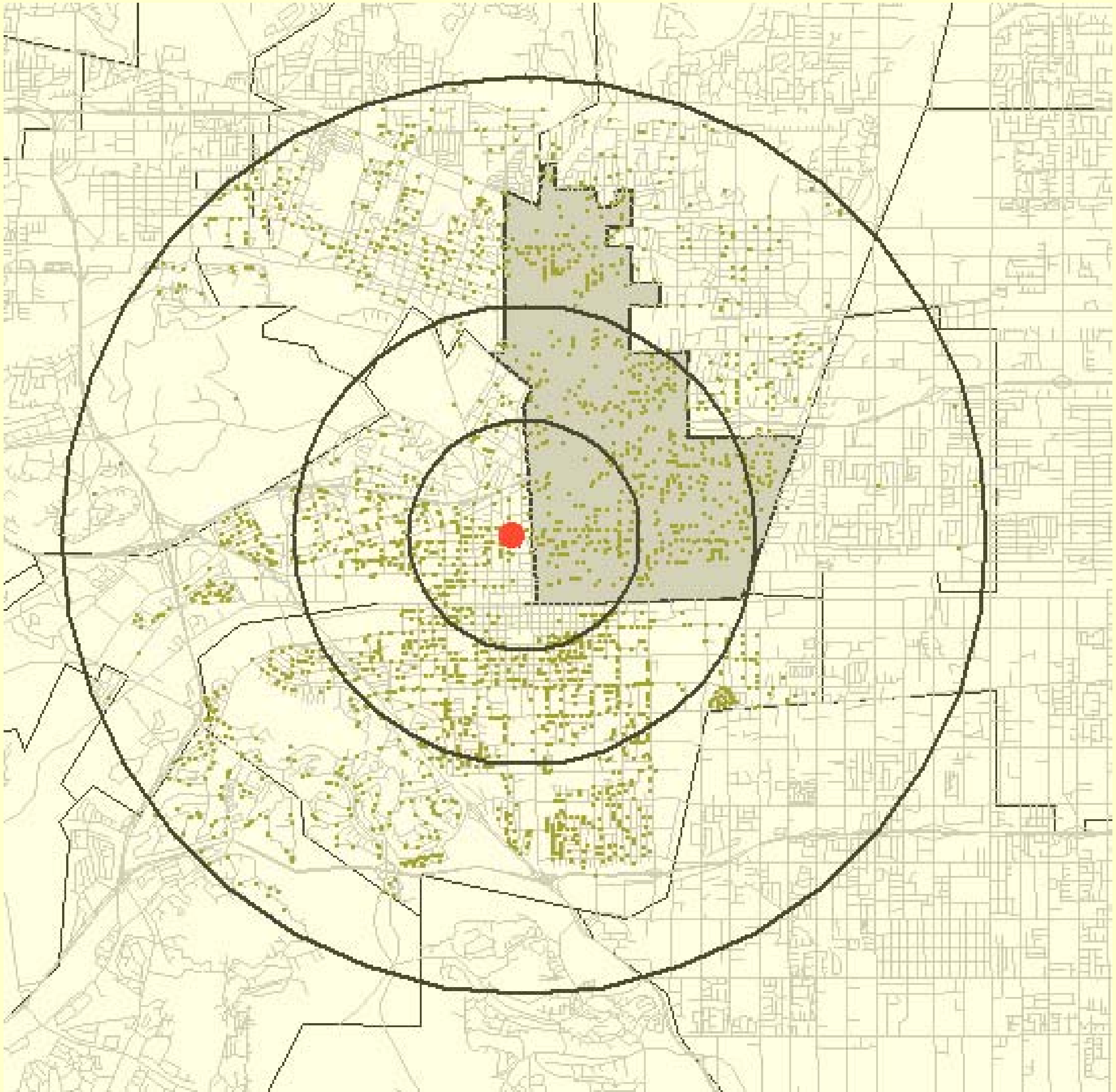
List of Pollutants Monitored by SCAQMD Stations



Map of CO-only (blue) and CO&PM10 (green) stations in LA County



Example of geocoded (random) residences at 1, 1-2, 2-4 mile distances from a monitoring station



CO –Term LBW

(Singleton births only)

CO – Third Trimester	
	Odds Ratio (95% CI)
Zip Code Level (LA County stations)	(n=2,001; 81,892)
$\geq 75^{th}$ quartile ($\geq$1.94 ppm)	**1.28 (1.10-1.50)**
Address Level	
Homes within <1 mile radius	(n=653; 28,144)
$\geq 75^{th}$ quartile ($\geq$1.8 ppm)	**1.36 (1.04-1.76)**
Homes within 1-2 mile radius	(n=2,077; 87,049)
$\geq 75^{th}$ quartile ($\geq$1.8 ppm)	**1.10 (0.95-1.28)**
Homes within 2-4 mile radius	(n=6,888; 293,904)
$\geq 75^{th}$ quartile ($\geq$1.8 ppm)	**1.08 (1.00-1.18)**

PM_{10} –Term LBW

(Singleton births only)

PM_{10} – Third Trimester	
	Odds Ratio (95% CI)
Zip Code Level (LA County stations) ≥75th quartile (≥45 ug/m^3)	(n=1,136; 47,839) **1.00 (0.83-1.20)**
Address Level	
Homes within <1 mile radius ≥75th quartile (≥44 ug/m^3)	(n=247; 10,981) **1.48 (1.00-2.19)**
Homes within 1-2 mile radius ≥75th quartile (≥45 ug/m^3)	(n=895; 40,803) **0.96 (0.78-1.18)**
Homes within 2-4 mile radius ≥75th quartile (≥45 ug/m^3)	(n=3,424; 146,347) **1.08 (0.97-1.20)**

PM_{10} – Preterm Birth
(Singleton Vaginal)

PM_{10} – 6 weeks prior to birth	
	Odds Ratio (95% CI)
Zip Code Level (LA County stations) ≥75^{th} quartile (≥45 ug/m^3)	(n=3,764; 37,934) **1.04 (0.96-1.14)**
Address Level	
Homes within 1 mile radius ≥75^{th} quartile (≥45 ug/m^3)	(n=734; 7,964) **1.12 (0.92-1.37)**
Homes within 2 mile radius ≥75^{th} quartile (≥45 ug/m^3)	(n=3,066; 32,293) **0.99 (0.89-1.10)**
Homes within 4 mile radius ≥75^{th} quartile (≥45 ug/m^3)	(n=12,282; 115,326) **0.98 (0.93-1.03)**

PM 2.5 - Preterm Birth
(Singleton Vaginal)

$PM_{2.5}$ – 6 weeks prior to birth	
	Odds Ratio (95% CI)
Zip Code Level (SoCAB stations) ≥75th quartile (≥25 ug/m^3)	(n=1,381; 14,047) **1.19 (1.02-1.40)**
Address Level	
Homes within 1 mile radius ≥75th quartile (≥24 ug/m^3)	(n=378; 3,778) **1.25 (0.93-1.68)**
Homes within 2 mile radius ≥75th quartile (≥25 ug/m^3)	(n=1,185; 12,170) **1.04 (0.87-1.24)**
Homes within 4 mile radius ≥75th quartile (≥25 ug/m^3)	(n=5,229, 48,855) **1.08 (0.99-1.17)**

CO only stations – Preterm Birth
(Singleton Vaginal)

CO – 6 weeks prior to birth	
	Odds Ratio (95% CI)
Address Level	
Homes within <1 mile radius $\geq 75^{th}$ quartile ($\geq$2 ppm)	(n=1 283; 13 329) **1.32 (1.03-1.70)**
Homes within 1-2 mile radius $\geq 75^{th}$ quartile ($\geq$2 ppm)	(n=3 602; 35 817) **1.37 (1.18-1.59)**
Homes within 2-4 mile radius $\geq 75^{th}$ quartile ($\geq$2 ppm)	(n=12 069, 114 684) **1.04 (0.95-1.13)**

Note: no CO effect observed at stations monitoring PM

Results

- CO results
  - Term LBW risk same as seen before but stronger close to a station
  - Preterm birth risk only increased at CO-only stations
- PM_{10}
  - Term LBW and preterm birth association only seen close to a station
- $PM_{2.5}$
  - Not enough data for Term LBW near stations
  - Results for preterm birth are most similar to those seen for CO at CO only stations

Conclusions

- 1994-2000 similar to 1989-1993 results even though air pollution concentrations decreased (at least for CO)
- PM2.5 results need further follow-up
- Geocoding strengthens effects: areas within 1 miles of a monitoring station show generally larger effect sizes for CO and PM10, PM2.5

UCLA-**E**nvironment and **P**regnancy **O**utcome **S**tudy

- NIEHS funded study 1R01ES013717
- Survey mothers who gave births to LBW/Preterm infants and normal weight/term controls
- Goal:
  - Collect information on
    - indoor pollution sources
    - in-transit exposures
    - Individual level risk factors during pregnancy including: time-activity, smoking, alcohol, diet, occupation, psychosocial stress
  - Use this information to adjust evaluate confounding employing a two-stage design

UCLA-**E**nvironment and **P**regnancy **O**utcome **S**tudy

- Cohort of infants born 1/1/03-12/31/03 to residents of 111 Los Angeles County zip codes (n=58,316)
  - Located near a SCAQMD monitoring station (n=24 zip codes, 100% of cases) or a major roadway (n=87 zip codes, sampled randomly 30% of cases); randomly sampled 1 control for each case from same zip code
  - Interviewed selected mothers 3-6 months after birth
    - n = 6374 eligible individuals, n = 2544 responders (40%)
- Outcome: term and preterm low birthweight = infant weighed <2500g at delivery

UCLA-EPOS study

- Birth Cohort:
  - Women and infants identified through California State birth records
- Case-control:
  - Nested case-control sample drawn from this cohort for the UCLA-EPOS Study

- Data: infant birth records from LA County and the State
  - Maternal address geocoded to determine census tract and nearest ambient air monitoring station
  - Daily exposure levels used to calculate average exposure by month, trimester, and gestation period

UCLA-EPOS study: data sources

- Infant birth records
- Air monitoring station data
- EPOS survey questionnaires

Covariates from 2 data sources

- From birth records: birth outcomes, maternal address, usual covariates
- From EPOS case-control study interview: **detailed covariate data**, incl. maternal smoking, drinking, marital status, income, stress, partner support, nutrition, infections and medications during pregnancy

Description of the Cohort and the EPOS responders

		Cohort n= 59,025	EPOS responders n = 2546
Maternal age	< 20	5773 (10%)	270 (11%)
	20 - < 35	43,427 (74%)	1866 (73%)
	35 +	9811 (17%)	410 (16%)
	Missing	*14*	*0*
Maternal race	White	9283 (16%)	433 (17%)
	Hispanic	39,256 (67%)	1693 (67%)
	African-American	4193 (7%)	185 (7%)
	Asian/PI	5468 (9%)	190 (8%)
	Other	529 (1%)	32 (1%)
	Missing	*296*	*13*
Maternal parity	Multiparous	35,426 (60%)	1524 (60%)
	Primaparous	23,570 (40%)	1019 (40%)
	Missing	*20*	*3*
Maternal education (years)	< 12	22,472 (39%)	882(35%)
	12 +	35,519 (61%)	1621 (65%)
	Missing	*1034*	*43*
Season of birth	Winter	14,224 (24%)	611 (24%)
	Spring	15,736 (24%)	614 (24%)
	Summer	14,855 (25%)	679 (27%)
	Fall	14,210 (24%)	642 (25%)
	Missing	*11*	*0*
CO exposure	< 1 ppm	40,698 (69%)	1699 (67%)
	1-2 ppm	18,284 (31%)	847 (33%)
	Missing	*43*	*0*
Birthweight	Normal birthweight	55,804 (95%)	2012 (79%)
	Low birthweight	3210 (5%)	531 (21%)
	Missing	*11*	*3*

Description of the EPOS responders, by birth weight category

		Low Birthweight n=531	Normal Birthweight n=2012
Maternal smoking	Never	359 (70%)	1401 (71%)
	Before pregnancy	127 (25%)	509 (26%)
	During pregnancy	29 (6%)	76 (4%)
	Missing = 46		
Drank alcohol during pregnancy	Yes	46 (9%)	133 (7%)
	No	465 (91%)	1788 (93%)
	Missing = 116		
Lived in house with a smoker during pregnancy	Yes	128 (24%)	338 (17%)
	No	399 (76%)	1649 (83%)
	Missing = 32		
Married/living with partner	Yes	400 (76%)	1599 (80%)
	No	126 (24%)	398 (20%)
	Missing = 23		
Income < $10,000 per year	Yes	116 (26%)	398 (24%)
	No	323 (74%)	1287 (76%)
	Missing = 422		
Income $75,000 + per year	Yes	76 (17%)	261 (15%)
	No	363 (83%)	1424 (85%)
	Missing = 422		

Description of the EPOS responders, by entire-pregnancy CO exposure

		< 1 ppm n = 1699	1 - <2 ppm n = 847
Maternal smoking	Never	1150 (69%)	613 (73%)
	Before pregnancy	444 (27%)	192 (23%)
	During pregnancy	74 (4%)	30 (4%)
	Missing = 43		
Drank alcohol during pregnancy	Yes	129 (8%)	51 (6%)
	No	1495 (92%)	760 (94%)
	Missing = 113		
Lived in house with a smoker during pregnancy	Yes	293 (17%)	173 (21%)
	No	1385 (83%)	666 (79%)
	Missing = 29		
Married/living with partner	Yes	1367 (81%)	635 (76%)
	No	322 (19%)	202 (24%)
	Missing = 20		
Income < $10,000 per year	Yes	319 (22%)	195 (28%)
	No	1109 (78%)	504 (72%)
	Missing = 419		
Income $75,000 + per year	Yes	249 (17%)	88 (13%)
	No	1179 (83%)	611 (87%)
	Missing = 419		

Analysis 1:
Phase 1 variables only--
stratification based on exposure

Covariates included in the models:

Phase 1: maternal age, race, parity, education, quarter of birth

Association for CO exposure (OR & 95% CI) and LBW:

1. Birth cohort: 1.15 (1.06 – 1.25)
2. Case-control: 1.33 (1.06 – 1.68)

Using two-phase estimators to account for sampling from birth cohort

1. WL estimate: 1.19 (1.05 – 1.34)
2. PL estimate: 1.20 (1.06 – 1.35)
3. ML estimate: 1.20 (1.07 – 1.34)

Phase 1 and Phase 2 variables--
Compare case-control and two-phase CO and LBW results

Covariates included in the models:

Phase 1: maternal age, race, parity, education, quarter of birth

Phase 2: maternal smoking during pregnancy, alcohol consumption, residence in house with a smoker, marital/partner status

Case-control:	1.32	(1.05 – 1.66)
WL:	1.13	(1.03 – 1.25)
PL:	1.14	(1.01 – 1.29)

Adjusted OR (95% CI) for EPOS responders, based on EPOS survey data

Entire Pregnancy: 1 – 2 ppm vs. < 1 ppm	1.3 (1.1; 1.6)	1.4 (1.0; 1.9)	1.2 (1.0; 1.6)	1.2 (1.0; 1.6)	1.3 (1.0; 1.6)	1.3 (1.0; 1.6)
Maternal smoking Never Before pregnancy During pregnancy	 1.0 1.0 (0.8; 1.2) 1.5 (1.0; 2.4)					
Drank alcohol during pregnancy		1.4 (1.0; 1.9)				
Lived in house with a smoker during pregnancy			1.6 (1.2; 2.0)			
Married/living with partner				0.8 (0.6; 1.0)		
Income < $10,000 per year					1.1 (0.9; 1.5)	
Income $75,000 + per year						1.2 (0.9; 1.5)

OR adj for all covariates simultaneously: 1.3 (1.0; 1.6)

Take Home Message

- Association between CO and low birth weight analogous to what has previously been shown
- Associations similar for cohort and EPOS responders
- Some differences between EPOS responders and non-responders, which seem due in part to measured covariates
- CO and LBW associations persist even after for adjusting for a range of individual-level risk factors
- Results from nested survey useful for adjusting models or for informing sensitivity analyses
- Lack of precision in results from EPOS responders suggests a need for two-stage analyses using the known case-control sampling fractions